Emerging therapeutic options for the treatment of patients with symptomatic asthma

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Objective: Asthma is a chronic inflammatory disorder of the airways with increasing worldwide prevalence. Despite treatment according to guidelines, a considerable proportion of patients with asthma remain symptomatic. Different potential therapeutic options for the treatment of these patients are currently in development and undergoing clinical trials, and it is important to regularly review their status.

Data Sources: A search of ClinicalTrials.gov was performed and supported by a PubMed literature search and restricted to the previous 10 years to ensure currency of data. The results were manually filtered to identify relevant articles.

Study Selections: Emerging therapies that are currently in phase 2 and 3 development include anti-immunoglobulin E or oral glucocorticosteroids is severe disease where control cannot be achieved add-on therapy with anti-immunoglobulin E or oral glucocorticosteroids is recommended to achieve control. In patients with more advanced, with data available from different phase 2 and 3 studies. Results demonstrate that it is an efficacious add-on to at least inhaled corticosteroid maintenance therapy across severities of symptomatic asthma.

Results: The clinical trial program of the long-acting muscarinic antagonist tiotropium is currently the most advanced, with data available from different phase 2 and 3 studies. Results demonstrate that it is an efficacious add-on to at least inhaled corticosteroid maintenance therapy across severities of symptomatic asthma.

Conclusion: The results of ongoing and future studies will help to determine whether these emerging therapeutic options will help address the unmet need for improvement in asthma management.

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treatment of symptomatic asthma, including anti-interleukin (IL) agents, chemokine receptor antagonists, phosphodiesterase-4 inhibitors, and long-acting muscarinic antagonists (LAMAs). The emerging anti-IL agents benralizumab, reslizumab, dupilumab, brodalumab, lebrikizumab, and mepolizumab, the CRTh2 antagonist OC000459, the phosphodiesterase-4 inhibitor roflumilast, and the LAMAs glycopyrronium bromide, umeclidinium bromide, and tiotropium bromide were identified for inclusion based on recent literature.

Search Strategy

A search of ClinicalTrials.gov was performed using the drug names listed earlier AND asthma as search terms (Table 1). A PubMed literature search also was performed using the Boolean string asthma [title/abstract] AND drug name [title/abstract] AND clinical trial [ptyp] and was restricted to the previous 10 years to ensure currency of data (June 2015). The results were manually filtered to identify relevant articles or studies with data from well-designed clinical trials of the treatment of interest in human patients.

Anti-IL Agents in the Treatment of Asthma

Anti-IL agents are monoclonal anticytokine agents that decrease airway inflammation and prevent eosinophil activation. The literature search provided 16 publications relating to the anti-IL agents benralizumab, reslizumab, dupilumab, brodalumab, lebrikizumab, and mepolizumab (eTable 1A).

Benralizumab

An initial phase 1 study in 27 patients with asthma found that single-dose intravenous and multiple-dose subcutaneous benralizumab (anti–IL-5) decreased airway, bone marrow, and peripheral blood eosinophil counts, with comparable safety profiles. In a phase 2 study in 108 patients with acute asthma, a single dose of intravenous benralizumab was found to decrease the rate (1.82 vs 3.59 [total number of exacerbations per total duration of person-year follow-up], P = .01) and severity (0.65 vs 1.62 [total number of exacerbations per total duration of person-year follow-up], P = .02) of asthma exacerbations compared with placebo and had an acceptable safety profile. Patients with severe asthma are currently being recruited for additional phase 3 studies (Table 1).

Reslizumab

In a study of 106 patients with severe eosinophilic asthma, treatment with monthly reslizumab infusions (anti–IL-5) showed a trend toward improved asthma control (P = .0541), significantly decreased sputum eosinophils (P = .0068), and significantly improved lung function, as measured by forced expiratory volume in 1 second (FEV1; P = .0023), percentage of predicted FEV1 (P = .0010), and forced vital capacity (FVC; P = .0054), compared with placebo. The results from the first phase 3 trials in 953 adult and adolescent patients (489 patients in study 1 and 464 patients in study 2) with moderate to severe eosinophilic asthma (NCT01287039 and NCT01285323) showed that monthly intravenous reslizumab significantly decreased the frequency of asthma exacerbations (P < .0001 in the 2 trials) and had a similar adverse-event profile compared with placebo. Additional phase 2 and 3 trials of reslizumab in adult and pediatric patients with eosinophilic asthma are currently ongoing (Table 1).

Dulipilumab

Dulipilumab (anti–IL-4) showed efficacy in a 12-week phase 2 trial of 104 patients with moderate to severe eosinophilic asthma (NCT01312961). Significant decreases in the incidence of asthma exacerbations (P < .001) and significant improvements in most measurements of lung function (FEV1, P < .001) and asthma control (5-question Asthma Control Questionnaire [ACQ-5], P = .001) were observed after once-weekly subcutaneous administration of 300 mg of dupilumab compared with placebo; dupilumab also was found to decrease biomarkers associated with T-helper type 2 (Th2)-driven inflammation. A phase 2 trial and follow-on phase 3 trial are currently ongoing to evaluate the efficacy and safety of different doses and treatment regimens of dupilumab in patients with moderate to severe asthma (Table 1).

Brodalumab

In a phase 2 dose-ranging study in 302 adult patients with moderate to severe asthma (NCT011992289), no treatment differences were observed in 7-question ACQ (ACQ-7) scores, lung function, or asthma symptoms after subcutaneous brodalumab (anti–IL-17) at 140, 210, or 280 mg or placebo. Prespecified subgroup analyses showed an improvement in ACQ-7 score beyond the minimal clinically important difference after 210 mg of brodalumab only (P = .02; no adjustment for multiplicity) in patients with high bronchodilator reversibility (post-bronchodilator FEV1 improvement ≥20%). A second phase 2 study of brodalumab in patients with high bronchodilator reversibility is currently recruiting patients (Table 1).

Lebrikizumab

Lebrikizumab (anti–IL-13) at 250 mg, administered subcutaneously every 4 weeks, showed improved lung function in a phase 2 study in 204 patients with asthma (NCT01350838) and decreased eosinophils in the blood, sputum, and nasal wash, with an acceptable safety profile. More patients showed a decrease in sputum eosinophils with lebrikizumab than with placebo (background treatment with inhaled corticosteroids and long-acting β2-agonists; P < .05). Additional phase 2 and 3 trials of lebrikizumab are currently ongoing (Table 1).

Table 1

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Abbreviation: CRT12, chemoattractant receptor-homologous molecules expressed on T-helper type 2 lymphocytes.
trial in 219 adult patients with inadequately controlled asthma despite medium- to high-dose ICS therapy (NCT00930163). Improvements in FEV₁ were significant compared with placebo (P = .02), with greater improvements observed in patients with high serum-periostin levels. In a second phase 2 trial in 212 patients with asthma not receiving ICS (NCT00971035), monthly subcutaneous administration of lebrikizumab at 125, 250, or 500 mg did not provide any meaningful improvements in lung function. In a third phase 2 trial in 29 adult patients with mild allergic asthma (NCT00781443), monthly lebrikizumab treatment decreased the late asthmatic response (FEV₁ decrease ≥15% 2–12 hours after allergen challenge) by 48% compared with placebo, with exploratory analyses showing that patients with allergic asthma exhibited a greater decrease compared with those with nonallergic asthma. Additional phase 2 studies of lebrikizumab in the treatment of asthma are ongoing, with phase 3 studies currently recruiting patients (Table 1).

**Mepolizumab**

Studies in patients with severe eosinophilic asthma showed that mepolizumab (anti–IL-5) decreased exacerbation risk, improved quality of life, lowered eosinophil counts, improved asthma control, and improved lung function. In a phase 2 trial of 621 patients (NCT01000506), treatment with intravenous mepolizumab significantly lowered the rate of clinically significant exacerbations (48% decrease in the 75-mg group, 39% decrease in the 250-mg group, 52% decrease in the 750-mg group, P < .0005 for all comparisons) compared with placebo. In a parallel-group trial of 61 patients with refractory eosinophilic asthma, monthly treatment with 750 mg of intravenous mepolizumab was associated with fewer severe exacerbations (P = .02), lower blood (P < .001) and sputum (P = .002) eosinophil counts, and significant improvements in quality of life (P = .02) over 1 year compared with placebo, although no significant improvements in asthma symptoms, FEV₁, or airway hyper-responsiveness were observed between treatment groups. After cessation of mepolizumab treatment, an increase in blood eosinophil count, severe exacerbation frequency, and asthma symptoms was observed. In a phase 2 parallel-group study of 20 patients with corticosteroid-dependent eosinophilic asthma (NCT00292877), the proportion of patients who experienced an asthma exacerbation was significantly decreased (P = .008); there also were significant decreases in sputum (P = .005) and blood (P = .004) eosinophil levels and a significant improvement in asthma control (P = .01) after 750 mg of intravenous mepolizumab every 4 weeks. In a phase 3 study of 576 patients with severe eosinophilic asthma (NCT01691521), exacerbation rate was decreased by 47% and 53% and FEV₁ was increased by 100 and 98 mL (P < .005 for all comparisons) in patients receiving 75 mg of intravenous mepolizumab and 100 mg of subcutaneous mepolizumab monthly, respectively, with significant improvements also observed in asthma control. In a second phase 3 study in 135 patients with severe eosinophilic asthma, after treatment with 100 mg of subcutaneous mepolizumab every 4 weeks, there was a 32% decrease in exacerbation rate and a decrease of 0.52 in ACQ-5 score, with the decrease in background ICS use 2.39 times greater than in the placebo treatment group. Conversely, in a study by Flood-Page et al of 362 patients with moderate symptomatic asthma, no significant clinical benefit was observed in lung function, rescue medication use, asthma symptoms, exacerbation rate, or quality of life after 3 intravenous infusions of 250 or 750 mg of mepolizumab at monthly intervals. In a subset of 37 patients from this study, significant decreases in sputum and blood eosinophils were observed after treatment with 250 and 750 mg of intravenous mepolizumab every 4 weeks (sputum, P = .006 and P = .004, respectively; blood, P < .001 for the 2 doses). Several additional phase 2 and 3 studies of mepolizumab in the treatment of patients with severe eosinophilic asthma are ongoing but have yet to report data (Table 1).

**CRTh2 Antagonists in the Treatment of Asthma**

The CRTh2 is a G-protein–coupled receptor that mediates the activation of Th2 lymphocytes, eosinophils, and basophils in response to prostaglandin D₂. Airway prostaglandin D₂ levels are elevated in patients with asthma after an allergen challenge, suggesting a role in Th2-mediated allergic inflammation, and therefore CRTh2 antagonists might inhibit the activation of lymphocytes, eosinophils, and basophils and decrease the asthma allergic response. Three publications related to OC000459 were identified (eTable 1B), which is currently in phase 2 development (Table 1).

**OC000459**

A phase 2 study of twice-daily OC000459 at 200 mg (NCT01057927) showed significantly improved quality of life (P = .0113) and nocturnal symptoms (P = .008) compared with placebo in 132 patients with moderate persistent asthma. Improvements in FEV₁ and sputum eosinophil count also were observed but were not statistically significant. In a 2-way phase 2 crossover study of 21 steroid-naïve patients with asthma (NCT01056692), treatment with twice-daily OC000459 at 200 mg was found to significantly inhibit the late asthmatic response to allergen challenge (P = .018) and significantly reduce the post–allergen increase in sputum eosinophils (P = .002); OC000459 treatment had no effect on the early asthmatic response to allergen challenge. In a phase 2 dose-finding study of OC000459 once daily at 25 or 200 mg or twice daily at 100 mg in 519 patients with mild to moderate persistent asthma (NCT00890877), a significant improvement in FEV₁ was observed after treatment with the once-daily 25-mg dose (P = .028). Significant improvements also were observed in ACQ-7 (P = .001) and Asthma Quality of Life Questionnaire (P = .002) scores, and there was a nonsignificantly lower incidence of exacerbations and a significant decrease in respiratory infections (P = .003), in patients treated with OC000459 compared with placebo.

**Phosphodiesterase-4 Inhibitors in the Treatment of Asthma**

Phosphodiesterases are involved in the degradation of cyclic adenosine monophosphate, a natural modulator of inflammation, which results in increased activity of inflammatory cells involved in the etiology of asthma, including T lymphocytes, eosinophils, macrophages, mast cells, monocytes, and neutrophils. Inhibition of phosphodiesterase activity results in maintenance of cyclic adenosine monophosphate levels and subsequent downregulation of inflammatory processes in cells involved in the pathophysiology of asthma. The PubMed literature search provided 6 publications related to roflumilast in the treatment of asthma (eTable 1C), with phase 2 and 3 trials ongoing (Table 1). Roflumilast is approved for use in the treatment of chronic obstructive pulmonary disease, and anti-inflammatory effects have been observed in patients with asthma. Roflumilast

**Roflumilast**

Treatment with roflumilast has been shown to significantly improve the late asthmatic response compared with placebo. In a 2-period crossover study in 13 patients with mild allergic asthma, treatment with a single dose of 1,800 μg of roflumilast significantly improved the late asthmatic response to a histamine challenge (P = .005). A 3-period crossover study of 23 patients with mild asthma showed that once-daily treatment with 250 or 500 μg of roflumilast significantly decreased the early (P = .0110 and P = .0009, respectively) and late (P = .0038 and P = .0046, respectively) asthmatic reactions to allergens. Further, in a phase 2 trial of 25 patients with mild allergic asthma (NCT01365533), 500 μg of roflumilast once daily inhibited the allergen-induced late-phase response (maximum percentage decrease in FEV₁, P = .02).
Improvements in lung function also have been reported after treatment with roflumilast. In a double-blinded, parallel-group trial of 693 adolescent and adult patients with mild to moderate asthma, treatment with once-daily roflumilast at 100, 250, or 500 µg significantly improved FEV₁ (P < .001 for all comparisons), with the 500-µg dose providing the greatest improvements. Morning and evening peak expiratory flow also were improved (P < .006 for all comparisons) compared with placebo. In a noninferiority study of 499 adolescent and adult patients with persistent asthma, once-daily roflumilast at 500 µg was found to provide comparable improvements in FEV₁ and FVC compared with treatment with twice-daily beclomethasone dipropionate at 200 µg.

In addition to showing efficacy in adult and adolescent patients with asthma, roflumilast has shown efficacy in pediatric patients with asthma. A 2-period ascending-dose study in 13 children and 12 adolescents with mild to moderate asthma found that roflumilast was well tolerated and that pharmacokinetic parameters were similar to those observed in adults.

**LAMAs in the Treatment of Asthma**

The short-acting muscarinic antagonists ipratropium bromide and omeprazolium bromide have been used in the treatment of asthma for several years; however, their widespread use has been limited because they are considered less effective than short-acting β₂-agonists. LAMAs block muscarinic acetylcholine receptors to impact on airway tone, smooth muscle contraction, mucus secretion, and vaso-dilation. LAMAs have not been thoroughly investigated in asthma because of the perception that they provide little bronchodilation above that induced by LABAs. This view has now changed, and some LAMAs are being investigated in clinical trials of asthma, including glycopyrrolate, umecillinium, and tiotropium.

A small phase 3 crossover study in 10 patients with asthma demonstrated that glycopyrrolate significantly prolonged broncholatation and bronchoprotection compared with ipratropium. A double-blinded crossover study of umecillinium monotherapy in 350 patients with asthma found no conclusive therapeutic benefit in patients not receiving ICS. However, the results of a double-blinded crossover study of ICS and umecillinium combination therapy in 421 patients with asthma showed improvements in trough FEV₁ (26–55 mL) and morning (15.9–22.9 L/min) and evening (16.2–28.8 L/min) peak expiratory flow compared with ICS alone.

The tiotropium clinical trial program is currently the most advanced, and tiotropium, delivered through the Spiriva HandiHaler device, has recently been incorporated into the Global Initiative for Asthma 2015 treatment guidelines as a recommended alternative therapy at steps 4 and 5 in adult patients with a history of exacerbations.

Data from 14 studies of tiotropium in asthma are reviewed below in more detail.

**Tiotropium**

Tiotropium, a long-acting anticholinergic bronchodilator, is currently approved by the US Food and Drug Administration for the treatment of patients with chronic obstructive pulmonary disease. It also has recently been approved for use in the treatment of asthma in the European Union and other countries worldwide. Further, it is currently under evaluation in the United States and other countries for the treatment of patients with asthma.

Early proof-of-concept studies in small numbers of patients indicated that tiotropium, delivered through the Spiriva HandiHaler device, provides sustained bronchodilatation and protection against bronchoconstriction. A study by Fardon et al. in 26 patients with severe asthma demonstrated that once-daily tiotropium at 18 µg provided significant improvements in lung function. Tiotropium at 18 µg also was shown to provide significant protection against methacholine challenge in a study of 10 patients with asthma and mild to moderate airway hyperresponsiveness. Sposato et al. demonstrated that 18 µg of tiotropium provided greater protection against methacholine-induced bronchoconstriction than ipratropium bromide, with similar improvements in FEV₁ compared with omeprazolium bromide, in a study of 44 patients with asthma.

In the large 3-way crossover Tiotropium Bromide as an Alternative to Increased Inhaled Corticosteroid in Patients Inadequately Controlled on a Lower Dose of Inhaled Corticosteroid (TALC) study in 210 patients with uncontrolled asthma (NCT00565266), once-daily tiotropium at 18 µg (through the Spiriva HandiHaler) significantly improved asthma symptoms (P < .001) and lung function (morning and evening peak expiratory flow, P < .001; FEV₁, P = .004) compared with a doubling of the ICS dose and was noninferior to salmeterol in patients with symptomatic asthma. A prespecified analysis of the TALC study data showed that a large number of patients who responded to treatment with albuterol and had increased airway obstruction demonstrated improved lung function after treatment with tiotropium.

Recent studies in patients with symptomatic asthma have evaluated the efficacy of once-daily tiotropium delivered by the Respimat Soft Mist inhaler (hereinafter referred to as tiotropium Respimat; Boehringer Ingelheim, Ingelheim am Rhein, Germany; Fig 1). The Respimat inhaler provides increased aerosol production time compared with pressurized metered-dose inhalers and dry-powder inhalers, which could benefit patients with low inspiratory capacity or poor timing of inhalation to actuation.

Phase 2 trials have examined the efficacy and safety of different doses and dosing regimens of tiotropium Respimat. Tiotropium at 10 and 5 µg as add-on to high-dose ICS plus LABA, taken each morning (NCT00365560), significantly improved peak FEV₁ (P < .0001 for all comparisons) and trough FEV₁ (P < .0004 for all comparisons) compared with placebo in 107 patients with severe symptomatic asthma. Adverse events were balanced across treatment groups, apart from dry mouth, which had a higher incidence in the 10-µg tiotropium treatment group (6.8%; 1.9% in the 5-µg group and 1.0% in the placebo group). One-daily evening dosing of tiotropium at 5, 2.5, and 1.25 µg as add-on to medium-dose ICS in 149 patients with moderate persistent asthma (NCT01233284) resulted in statistically significant improvements in lung function (peak FEV₁ within 3 hours after the dose [peak FEV₁(0–3h)], trough FEV₁, FEV₁ area under the curve [AUC(0–3h)], trough FVC, and AUC(0–3h)] of the 5-µg dose associated with the greatest improvements in all measurements. Improvements in lung function were found to be significant and equally well sustained for once-daily tiotropium at 5 µg (morning dosing) and twice daily at 2.5 µg (morning and evening dosing) as add-on to medium-dose ICS in a study of 94 patients with moderate symptomatic asthma (NCT01152450). In a study of 388 patients with moderate asthma with the B16-Arg/Arg genotype (NCT00350207), treatment with a once-daily evening dose of 5 µg of tiotropium was found to be superior to matching placebo (P < .05) and as efficacious as twice-daily salmeterol (P = .002) at maintaining improved lung function.

Phase 3 trials have examined the efficacy, safety, and tolerability of tiotropium Respimat in patients across severities of symptomatic asthma, as defined by ICS dose. In 2 randomized, double-blinded, 48-week, parallel-group trials with identical designs (NCT00772538 and NCT00776894), 912 patients with poorly controlled asthma received 5 µg of tiotropium once daily on placebo each morning as add-on to high-dose ICS plus LABA. Treatment with 5 µg of tiotropium significantly improved peak and trough FEV₁ (P < .01 for the 2 end points in the 2 trials) and increased the time to the first severe asthma exacerbation by 56 days, with a decrease of 21% in the risk of experiencing a severe exacerbation (pooled data, P = .03), compared with placebo. In 2 randomized, double-blinded, double-dummy, parallel-group trials with identical design...
Figure 1. Overview of lung function results from clinical trials of tiotropium Respimat in adults with asthma: (A) peak forced expiratory volume in 1 second; (B) trough forced expiratory volume in 1 second; (C) morning peak expiratory flow; (D) evening peak expiratory flow. Error bars represent SE. *Measured at week 8.59 bMeasured at week 4.60 cMeasured at the end of each 4-week treatment period.61 dMeasured at week 16.62 eMeasured at week 24.63 fPooled data; measured at week 24.64 gMeasured at week 52.65 *P < .05; ***P < .001.
(NCT01172808 and NCT01172821), 2,100 patients with moderate symptomatic asthma received 5 or 2.5 μg of tiotropium, or salmeterol or placebo, as add-on to medium-dose ICS. Because the results were highly comparable between studies, the investigators presented pooled data. Significant improvements in peak and trough FEV₁ were observed (P < .001 for all comparisons), with a larger proportion of ACQ-7 responders observed after 24 weeks of treatment with the tiotropium doses (5 μg, odds ratio 1.32, P = .035; 2.5 μg, odds ratio 1.33, P = .031), compared with placebo.64

Tiotropium Respimat was found to have safety and tolerability that were comparable with those of placebo in all trials in which they were assessed.59–65 In a long-term study of 5 or 2.5 μg of tiotropium or placebo once daily as add-on to medium-dose ICS with or without a LABA each evening in 285 Japanese patients (NCT01340209), the safety and tolerability (primary end point of the study) of tiotropium were found to be comparable with those of placebo.65

The first results from studies of tiotropium Respimat in adolescents and children are available. A phase 2, incomplete-crossover, dose-ranging study of 5, 2.5, and 1.25 μg of tiotropium as add-on to medium-dose ICS with or without a leukotriene receptor antagonist was conducted in 105 adolescent patients 12 to 17 years old with moderate symptomatic asthma (NCT01122680). Measurements of peak FEV₁(0–3h) (P = .0004), trough FEV₁ (P < .0001), and FEV₁ AUC(0–3h) (P = .001) were significantly improved after treatment with 5 μg of tiotropium.65 In a second phase 2 study of identical design in 101 children 6 to 11 years old with moderate symptomatic asthma (NCT01383499), significant improvements in measurements of peak FEV₁(0–3h) (P < .001 for all comparisons), trough FEV₁ (P < .005 for all comparisons), and FEV₁ AUC(0–3h) (P < .005 for all comparisons) were observed after treatment with all doses of tiotropium.65 As in the trials in adult patients, tiotropium was found to have comparable safety and tolerability as placebo.66,67 Further phase 2 and 3 studies of tiotropium as add-on to at least ICS in adolescents and children as young as 1 year are in progress.

Conclusions

There is currently an unmet need in the treatment of asthma, with a significant proportion of patients remaining symptomatic despite treatment according to guidelines. Different additional therapeutic options are undergoing development for use in the treatment of asthma, including anti-IL agents, CRTh2 antagonists, phosphodiesterase-4 inhibitors, and LAMAs.

The tiotropium clinical trial program is currently the most advanced, with published data from different phase 2 and 3 randomized clinical trials in patients with asthma. Data from studies in adult and adolescent patients with asthma have shown that tiotropium is an efficacious add-on to at least ICS maintenance therapy, with comparable safety and tolerability as placebo. Tiotropium could offer an alternative treatment option, particularly for patients for whom current treatments are unsuitable or ineffective. In adult patients with severe asthma and a history of exacerbations, tiotropium has recently been recommended as an alternative therapeutic option at Global Initiative for Asthma steps 4 and 5.2

It should be considered that clinical trial efficacy is distinct from real-life effectiveness. A recent retrospective study in 2,042 patients with asthma highlighted that primary care physicians in the United Kingdom have been prescribing LAMAs for the treatment of asthma since 2002, predominantly as add-on therapy in older patients with poorly controlled asthma despite good treatment compliance, particularly in those who were current or former smokers.68 In this real-life patient population, the addition of tiotropium, as 18 μg through the HandiHaler device (93%) or 5 μg through the Respimat Soft Mist inhaler (7%), provided a significant decrease in the incidence of exacerbations and antibiotic prescriptions for lower respiratory tract infections and a significant increase in asthma control during the following year. Additional large studies of data from real-life asthma populations will help to improve individualized patient care and will be useful to help determine the position of tiotropium in relation to current asthma treatment guidelines. Once fully indicated by regulatory authorities and incorporated into asthma treatment guidelines across age groups and disease severities, the use of tiotropium in the treatment of asthma might become more widespread, given its availability in pharmacies and physicians’ familiarity with using it to treat patients with chronic obstructive pulmonary disease.

Cost-effectiveness also is an important consideration in relation to real-life utility of treatments and deciding their relative place in therapeutic guidelines. This is particularly the case for biological therapies that target specific cytokines, which might require biomarker analyses to select the correct patients for treatment; such biomarker analyses are not required before treatment with tiotropium. In the first analysis of the cost-effectiveness of tiotropium, Willson et al.69 concluded that tiotropium provided a cost-effective treatment option in adult patients with severe asthma, as add-on to high-dose ICS plus LABA therapy. Further cost-effectiveness analyses, across age ranges and severities of asthma, could help to determine whether tiotropium add-on therapy provides an affordable treatment option that addresses the current unmet need in asthma treatment.

The clinical development of other emerging therapeutic options is less advanced compared with tiotropium; however, anti-IL agents, CRTh2 antagonists, phosphodiesterase-4 inhibitors, and other LAMAs also might provide additional options for the treatment of asthma. The results of ongoing and future randomized clinical trials of these and other agents will help to address the current unmet need in patients with symptomatic asthma and to determine where these emerging therapeutic options will fit in future asthma treatment guidelines.

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Supplementary Data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.anai.2015.07.011.

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<td>Castro et al, 2011&lt;sup&gt;3&lt;/sup&gt;</td>
<td></td>
<td>infusions of reslizumab 3 mg/kg or placebo (0.9% saline) every 4 wk</td>
<td>ND</td>
<td>randomized, double-blinded, placebo-controlled, 15-wk study</td>
<td>106 patients 18–75 y old with severe eosinophilic asthma</td>
<td>high-dose ICS (fluticasone ≥440 μg BID) + ≥1 other agent (including SABA, LABA, leukotriene antagonist, and cromolyn sodium)</td>
<td>ACQ-7&lt;sup&gt;4&lt;/sup&gt;, FEV&lt;sub&gt;1&lt;/sub&gt;, % predicted FEV&lt;sub&gt;1&lt;/sub&gt;, FVC, blood and sputum eosinophils, incidence of asthma exacerbations</td>
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<tr>
<td>Castro et al, 2015&lt;sup&gt;4&lt;/sup&gt;; NCT01287039 and NCT01285323</td>
<td></td>
<td>intravenous reslizumab 3 mg/kg or placebo every 4 wk</td>
<td>3</td>
<td>replicate randomized, double-blinded, placebo-controlled, parallel-group, 1-y studies</td>
<td>953 patients 12–75 y old with blood eosinophils ≥400 cells/μL and ≥1 exacerbation in previous year</td>
<td>medium- to high-dose ICS (fluticasone ≥440 μg QD) + another controller (LABA, oral corticosteroids, leukotriene modifiers, and cromolyn sodium)</td>
<td>annual frequency of exacerbations&lt;sup&gt;3&lt;/sup&gt;, FEV&lt;sub&gt;1&lt;/sub&gt;, ACQ-7, ASUJ, rescue medication use, blood eosinophil counts, AQLQ, adverse events</td>
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<td>Wenzel et al, 2013&lt;sup&gt;5&lt;/sup&gt;; NCT01312961</td>
<td></td>
<td>subcutaneous dupilumab 300 mg or placebo once weekly</td>
<td>2</td>
<td>randomized, double-blinded, placebo-controlled, parallel-group, 12-wk study</td>
<td>104 patients 18–65 y old with moderate to severe asthma and elevated eosinophil levels</td>
<td>medium- to high-dose ICS + LABA (fluticasone 250 or 500 μg and salmeterol 50 μg BID or equivalent) for 4 wk (LABA discontinued and ICS tapered during weeks 6–9)</td>
<td>incidence of asthma exacerbations&lt;sup&gt;5&lt;/sup&gt;, time to asthma exacerbation, FEV&lt;sub&gt;1&lt;/sub&gt;, PEF&lt;sub&gt;AM&lt;/sub&gt;, PEF&lt;sub&gt;PM&lt;/sub&gt;, ACQ-5, nocturnal waking, rescue medication use</td>
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<tr>
<td>Busse et al, 2013&lt;sup&gt;6&lt;/sup&gt;; NCT01195289</td>
<td></td>
<td>subcutaneous brodalumab 140, 210, or 280 mg or placebo at day 1 and weeks 1, 2, 4, 6, 8, and 10</td>
<td>2a</td>
<td>randomized, double-blinded, placebo-controlled, dose-ranging, 12-wk study</td>
<td>302 patients 18–65 y old with moderate to severe asthma</td>
<td>stable-dose ICS (fluticasone 200–1,000 mg QD or equivalent for ≥3 mo before screening) for ≥30 d medium- to high-dose ICS (fluticasone ≥200 and &lt;1,000 μg) ± LABA or leukotriene modifiers</td>
<td>ACQ-7&lt;sup&gt;6&lt;/sup&gt;, FEV&lt;sub&gt;1&lt;/sub&gt;, PEF&lt;sub&gt;AM&lt;/sub&gt;, rescue medication use, asthma symptom scores, symptom-free days, adverse events</td>
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<td>Corren et al, 2011&lt;sup&gt;7&lt;/sup&gt;; NCT00930163</td>
<td></td>
<td>subcutaneous lebrikizumab 250 mg or placebo every 4 wk</td>
<td>2</td>
<td>randomized, double-blinded, placebo-controlled, 24-wk study</td>
<td>219 adult patients with moderate to severe symptomatic asthma</td>
<td>medium- to high-dose ICS (fluticasone ≥200 and &lt;1,000 μg) ± LABA or leukotriene modifiers</td>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;&lt;sup&gt;7&lt;/sup&gt;, incidence of asthma exacerbations and severe exacerbations, PEF&lt;sub&gt;AM&lt;/sub&gt;, ACQ-5, rescue medication use</td>
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<td>Noonan et al, 2013&lt;sup&gt;8&lt;/sup&gt;; NCT00971035</td>
<td></td>
<td>4 doses of subcutaneous lebrikizumab 125, 250, or 500 mg or placebo every 4 wk</td>
<td>2</td>
<td>randomized, double-blinded, placebo-controlled, dose-ranging, 12-wk study</td>
<td>212 patients 18–65 y old with asthma not receiving ICS treatment</td>
<td>intermittent short-acting inhaled β&lt;sub&gt;2&lt;/sub&gt;-adrenergic agonists only</td>
<td>none</td>
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<td>Scheeren et al, 2014&lt;sup&gt;9&lt;/sup&gt;; NCT00781443</td>
<td></td>
<td>4 doses of subcutaneous lebrikizumab 5 mg/kg or placebo every 4 wk</td>
<td>2</td>
<td>randomized, double-blinded, placebo-controlled, parallel-group, 12-wk study</td>
<td>29 patients 18–55 y old with mild allergic asthma</td>
<td>intermittent short-acting inhaled β&lt;sub&gt;2&lt;/sub&gt;-adrenergic agonists only</td>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;&lt;sup&gt;9&lt;/sup&gt;, time to treatment failure, PEF&lt;sub&gt;AM&lt;/sub&gt;, PEF variability, reliever medication use, FEV&lt;sub&gt;1&lt;/sub&gt;&lt;sup&gt;9&lt;/sup&gt;, allergic challenge&lt;sup&gt;9&lt;/sup&gt;, adverse events, serum biomarkers, pharmacokinetics</td>
</tr>
<tr>
<td>Pavord et al, 2012&lt;sup&gt;10,11&lt;/sup&gt;; NCT01000506</td>
<td></td>
<td>13 infusions of intravenous mepolizumab 75, 250, or 750 mg or placebo (100 mL 0.9% NaCl) every 4 wk</td>
<td>1</td>
<td>randomized, double-blinded, placebo-controlled, parallel-group, 52-wk study</td>
<td>621 patients 12–74 y old with refractory eosinophilic asthma</td>
<td>fluticasone ≥880 μg (or equivalent) daily ± maintenance oral corticosteroids</td>
<td>incidence of asthma exacerbations&lt;sup&gt;10&lt;/sup&gt;, blood and sputum eosinophils, ACQ-6, quality of life</td>
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<td>Haldar et al, 2009&lt;sup&gt;12&lt;/sup&gt;; Haldar et al, 2014&lt;sup&gt;13&lt;/sup&gt;</td>
<td></td>
<td>12 infusions of intravenous mepolizumab 750 mg or placebo (150 mL 0.9% saline) every 4 wk</td>
<td>ND</td>
<td>randomized, double-blinded, placebo-controlled, parallel-group, 50-wk study</td>
<td>61 patients ≥18 y old with refractory eosinophilic asthma</td>
<td>high-dose corticosteroids</td>
<td>incidence of severe asthma exacerbations&lt;sup&gt;12&lt;/sup&gt;, ACQ-5, AQLQ, FEV&lt;sub&gt;1&lt;/sub&gt;, bronchodilator use, airway hyperresponsiveness, blood and sputum eosinophil counts</td>
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</table>
Nair et al, 2009; NCT00292877
5 infusions of intravenous mepolizumab 750 mg or placebo (normal saline diluent) every 4 wk
randomized, double-blinded, parallel-group, 26-wk study
20 adult patients with corticosteroid-dependent eosinophilic asthma
prednisone 5–25 mg and high-dose ICS (fluticasone 600–2,000 μg or equivalent)
decrease in prednisone dose, ACQ, FEV1, sputum and blood eosinophils
exacerbation rate, spirometry, hematology, ACQ-5, SGRQ, adverse events, vital signs

Ortega et al, 2014; NCT01691521
intravenous mepolizumab 75 mg, subcutaneous mepolizumab 100 mg, or placebo every 4 wk
randomized, double-blinded, double-dummy, 32-wk study
576 patients 12–85 y old with severe eosinophilic asthma
fluticasone propionate ≥880 μg (or equivalent) plus ≥3 mo of treatment with an additional controller
decrease in ICS use, rescue medication use, quality of life, incidence of asthma exacerbations, blood and sputum eosinophils

Bel et al, 2014; NCT01691508
subcutaneous mepolizumab 100 mg or placebo every 4 wk
randomized, double-blinded, parallel-group, 20-wk study
135 patients with severe eosinophilic asthma
high-dose ICS (prednisone 5–35 mg or equivalent) plus additional controller
exacerbation rate, spirometry, hematology, ACQ-5, SGRQ, adverse events, vital signs

Flood-Page et al, 2007
intravenous mepolizumab 250 or 750 mg or placebo every 4 wk
randomized, double-blinded, placebo-controlled, 12-wk study
362 patients 18–55 y old with moderate symptomatic asthma
increase in prednisone dose, decrease in ICS use, sputum eosinophils, serum IgE

B. Cyt2 antagonists
Barnes et al, 2012; NCT01057927
oral OC000459 200 mg BID or placebo
randomized, double-blinded, parallel-group, 4-wk study
132 steroid-free patients 18–55 y old with moderate persistent asthma
FEV1, PEF, asthma symptoms, quality of life, rescue medication use, sputum eosinophils, serum IgE

Singh et al, 2013; NCT01056692
oral OC000459 200 mg BID or placebo
randomized, double-blinded, placebo-controlled, 2-way crossover, 16-d study
21 steroid-naive patients 18–45 y old with allergic asthma
FEV1, PEF, asthma symptoms, quality of life, rescue medication use, sputum eosinophils, serum IgE

Petittiper et al, 2014; NCT00890877
oral OC000459 25 or 200 mg QD, 100 mg BID, or placebo
randomized, dose-finding, double-blinded parallel-group, 12-wk study
519 patients 18–55 y old with mild to moderate persistent asthma
PEFAM, PEFPM, asthma symptoms, rescue medication use, withdrawal owing to lack of efficacy

C. Phosphodiesterase-4 inhibitors
Louw et al, 2007
single dose of oral roflumilast 1,000 μg or placebo with 2- to 5-wk washout between the 2 treatment periods
randomized, double-blinded, 2-period, crossover study
13 patients 18–50 y old with mild allergic asthma
histamine challenge, allergen challenge

van Schalkwyk et al, 2005
oral roflumilast 250 or 500 μg or placebo QD for 7–10 d with washout periods of 2–5 wk between each treatment period
randomized, double-blinded, placebo-controlled, 3-period crossover study
23 patients 18–50 y old with mild asthma
allergen challenge, FEV1

Gauvreau et al, 2011; NCT01365533
oral roflumilast 500 μg or placebo QD
randomized, double-blinded, placebo-controlled, crossover, 14-d study
25 steroid-naive patients 18–54 y old with mild allergic asthma
allergen challenge, FEV1, methacholine challenge, sputum eosinophils, pharmacokinetic assessments

Bateman et al, 2006
oral roflumilast 100, 250, or 500 μg QD
randomized, double-blinded, parallel-group, 12-wk study
693 patients 15–70 y old with mild to moderate asthma
FEV1, PEFAM, PEFPM, asthma symptom scores, rescue medication use, withdrawal owing to lack of efficacy

Bousquet et al, 2006
oral roflumilast 500 μg QD or beclomethasone 200 μg BID
randomized, double-blinded, double-dummy, noninferiority, 12-wk study
499 patients 12–70 y old with persistent asthma
FEV1, FVC, PEF, AQLQ, ACQ-7, incidence of exacerbations and respiratory tract infections, rescue medication use, asthma symptoms, adverse events

Neville et al, 2008
single oral dose of roflumilast 100 μg in period 1 (3 d) and 250 μg in period 2 (4 d) with washout period of >14 d
open-label, crossover, 2-period, ascending-dose study
25 children and adolescents with mild to moderate asthma
methacholine challenge, adverse events

D. LAMAs
Hansel et al, 2005
single dose of inhaled glycopyrrolate 0.5, 1, or 2 mg, ipratropium 0.5 mg, and placebo with 7-d washout between treatments
randomized, double-blinded, placebo-controlled, 5-way crossover study
10 patients 18–60 y old with mild to moderate atopic asthma
methacholine challenge, adverse events

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<table>
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<tr>
<th>Study; trial number</th>
<th>Treatment arm</th>
<th>Phase</th>
<th>Study design</th>
<th>Patient population</th>
<th>Background medication</th>
<th>Key end points</th>
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<tr>
<td>Lee et al, 2015&lt;sup&gt;27&lt;/sup&gt;; NCT01641692</td>
<td>3 of 8 treatments: inhaled umclidinium 15.6, 31.25, 62.5, 125, or 250 μg QD and umclidinium 15.6 or 31.25 μg BID, or placebo for 14 d with 12- to 14-d washout between treatments</td>
<td>2</td>
<td>double-blinded, 3-period, crossover, incomplete-block study</td>
<td>350 patients ≥18 y old with asthma</td>
<td>none</td>
<td>trough FEV₁&lt;sub&gt;b&lt;/sub&gt;, PEFmax, PEF&lt;sub&gt;25&lt;/sub&gt;, rescue medication use, 0- to 24-h weighted mean FEV₁, adverse events, vital signs</td>
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<tr>
<td>Lee et al, 2015&lt;sup&gt;28&lt;/sup&gt;; NCT01573624</td>
<td>3 of 7 treatments: fluticasone furoate 100 μg alone QD, fluticasone furoate 100 μg QD + umclidinium 15.6, 31.25, 62.5, 125, or 250 μg QD or vilanterol 25 μg QD for 14 d with 12- to 14-d washout between treatments</td>
<td>2</td>
<td>double-blinded, 3-period, crossover, incomplete-block study</td>
<td>421 patients ≥18 y old with asthma</td>
<td>ICS</td>
<td>trough FEV₁&lt;sub&gt;b&lt;/sub&gt;, PEF&lt;sub&gt;25&lt;/sub&gt;, PEF&lt;sub&gt;Max&lt;/sub&gt;, rescue medication use, symptom-free days, adverse events, vital signs</td>
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<td>Fardon et al, 2007&lt;sup&gt;29&lt;/sup&gt;</td>
<td>inhaled fluticasone 500 μg BID + salmeterol 100 μg BID + tiotropium 18 μg (HandiHaler) QD or inhaled fluticasone 500 μg BID + salmeterol 100 μg BID + placebo</td>
<td>ND</td>
<td>randomized, double-blinded, placebo-controlled, 4-wk crossover study</td>
<td>26 patients ≥18 y old with severe asthma</td>
<td>none</td>
<td>FEV₁, FVC, PEF&lt;sub&gt;Max&lt;/sub&gt;, PEF&lt;sub&gt;25&lt;/sub&gt;, mini-AQLQ, body plethysmography</td>
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<tr>
<td>Terzano et al, 2004&lt;sup&gt;30&lt;/sup&gt;</td>
<td>single dose of inhaled tiotropium 18 μg (HandiHaler) or placebo</td>
<td>ND</td>
<td>comparative, 3-challenge study with 72-h washout between each challenge</td>
<td>10 patients with asthma and documented airway hyperresponsiveness</td>
<td>ND</td>
<td>methacholine challenge&lt;sup&gt;b&lt;/sup&gt;, FEV₁</td>
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<td>Sposato et al, 2008&lt;sup&gt;31&lt;/sup&gt;</td>
<td>single dose of inhaled ipratropium 40 μg, oxitropium 200 μg or tiotropium 18 μg (HandiHaler)</td>
<td>ND</td>
<td>comparative study after 72-h washout</td>
<td>44 patients with intermittent bronchial asthma</td>
<td>none</td>
<td>methacholine challenge&lt;sup&gt;b&lt;/sup&gt;, FEV₁</td>
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<td>Peters et al, 2010&lt;sup&gt;32&lt;/sup&gt;; Peters et al, 2013&lt;sup&gt;33&lt;/sup&gt;; NCT00350207</td>
<td>inhaled tiotropium 18 μg (HandiHaler) QD, beclomethasone 800 μg BID or placebo Respimat QD</td>
<td>ND</td>
<td>randomized, 3-way, double-blinded, triple-dummy, 14-wk crossover study</td>
<td>210 patients ≥18 y old with asthma</td>
<td>ICS (beclomethasone 80 μg BID)</td>
<td>PEF&lt;sub&gt;Max&lt;/sub&gt;, FEV₁, number of asthma-control days, asthma symptoms, rescue bronchodilator use, asthma exacerbations, use of health care services, biomarkers of airway inflammation, ACQ, asthma symptoms, AQLQ, adverse events</td>
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<td>Kerstjens et al, 2011&lt;sup&gt;34&lt;/sup&gt;; NCT00365560</td>
<td>inhaled tiotropium Respimat 10 or 5 μg or placebo Respimat QD (morning dosing)</td>
<td>2</td>
<td>randomized, double-blinded, 24-wk crossover study</td>
<td>107 patients 18–75 y old with severe persistent asthma</td>
<td>high-dose ICS (budesonide ≥800 μg or equivalent) + LABA (theophylline, leukotriene modifiers, and oral glucocorticosteroids also permitted in stable doses)</td>
<td>peak FEV₁&lt;sub&gt;(0−3h)&lt;/sub&gt;, trough FEV₁, peak FVC, trough FVC, FEV₁, AUC&lt;sub&gt;0−3h&lt;/sub&gt;, FVC AUC&lt;sub&gt;0−3h&lt;/sub&gt;, PEF&lt;sub&gt;Max&lt;/sub&gt;, PEF&lt;sub&gt;25&lt;/sub&gt;, asthma symptoms, rescue medication use, asthma symptom-free days, mini-AQLQ, adverse events, vital signs</td>
</tr>
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<td>Beeth et al, 2014&lt;sup&gt;35&lt;/sup&gt;; NCT01233294</td>
<td>inhaled tiotropium Respimat 5, 2.5, 1.25 μg or placebo Respimat QD (evening dosing)</td>
<td>2</td>
<td>randomized, double-blinded, placebo-controlled, dose-ranging, 4-way, 16-wk crossover study</td>
<td>149 patients 18–75 y old with moderate asthma</td>
<td>medium-dose ICS (budesonide 400–800 μg or equivalent)</td>
<td>peak FEV₁&lt;sub&gt;(0−3h)&lt;/sub&gt;, trough FEV₁, peak FVC, trough FVC, FEV₁, AUC&lt;sub&gt;0−3h&lt;/sub&gt;, FVC AUC&lt;sub&gt;0−3h&lt;/sub&gt;, PEF&lt;sub&gt;Max&lt;/sub&gt;, PEF&lt;sub&gt;25&lt;/sub&gt;, ACQ-7, adverse events, vital signs</td>
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<td>Timmer et al, 2015&lt;sup&gt;36&lt;/sup&gt;; NCT01152450</td>
<td>inhaled tiotropium Respimat 5 μg (evening), salmeterol HFA-MDI 50 μg BID (morning and evening), or placebo Respimat (morning and evening)</td>
<td>2</td>
<td>randomized, double-blinded, placebo-controlled, 12-wk crossover study</td>
<td>94 patients 18–75 y old with moderate symptomatic asthma</td>
<td>medium-dose ICS (budesonide 400–800 μg or equivalent)</td>
<td>peak FEV₁&lt;sub&gt;(0−3h)&lt;/sub&gt;, trough FEV₁, peak FVC, trough FVC, FEV₁, AUC&lt;sub&gt;0−3h&lt;/sub&gt;, FVC AUC&lt;sub&gt;0−3h&lt;/sub&gt;, PEF&lt;sub&gt;Max&lt;/sub&gt;, PEF&lt;sub&gt;25&lt;/sub&gt;, ACQ-7, pharmacokinetic assessments, adverse events</td>
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<td>Bateman et al, 2011&lt;sup&gt;37&lt;/sup&gt;; NCT00350207</td>
<td>inhaled tiotropium Respimat 5 μg QD (evening), salmeterol HFA-MDI 50 μg BID (morning and evening), or matching placebo</td>
<td>2</td>
<td>randomized, double-blinded, double-dummy, placebo-controlled, parallel-group, 16-wk study</td>
<td>388 patients 18–67 y old with moderate asthma with B16-Arg/Arg genotype</td>
<td>medium- to high-dose ICS (budesonide 400–1,000 μg or equivalent)</td>
<td>PEF&lt;sub&gt;Gen&lt;/sub&gt;, PEF&lt;sub&gt;PM&lt;/sub&gt;, FEV₁, asthma symptoms, rescue medication use, asthma symptom-free days, level of asthma control, adverse events, vital signs, mini-AQLQ</td>
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<tr>
<td>Study</td>
<td>Intervention</td>
<td>Dosing</td>
<td>n</td>
<td>Population Characteristics</td>
<td>Outcomes</td>
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<td>Kerstjens et al, 2012&lt;sup&gt;38&lt;/sup&gt;; NCT00772538 and NCT00776984</td>
<td>inhaled tiotropium Respimat 5 µg or placebo Respimat QD (morning dosing)</td>
<td>3</td>
<td>2 replicate randomized, double-blinded, placebo-controlled, parallel-group, 48-wk studies</td>
<td>912 patients 18–75 y old with poorly controlled asthma</td>
<td>high-dose ICS (budesonide ≥800 µg or equivalent) + LABA (continued use of stable-dose sustained-release theophylline, leukotriene modifiers, anti-IgE, and oral glucocorticoids ≤5 mg/d) was permitted; peak FEV&lt;sub&gt;1&lt;/sub&gt;(0–3h), trough FEV&lt;sub&gt;1&lt;/sub&gt;, time to first severe asthma exacerbation&lt;sup&gt;1&lt;/sup&gt;, 24-h FEV&lt;sub&gt;1&lt;/sub&gt; measurements, individual peak and trough FEV&lt;sub&gt;1&lt;/sub&gt; and FVC measurements, FEV&lt;sub&gt;1&lt;/sub&gt; AUC(0–3h), FVC AUC(0–3h), time to the first episode of asthma worsening, PEFA&lt;sub&gt;r&lt;/sub&gt;, PEFA&lt;sub&gt;p&lt;/sub&gt;, ACQ-7, ACQ-7 responder rate, adverse events, vital signs</td>
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<td>Kerstjens et al, 2015&lt;sup&gt;39&lt;/sup&gt;; NCT01172808 and NCT01172821</td>
<td>inhaled tiotropium Respimat 5 or 2.5 µg QD (evening dosing), salmeterol 50 µg HFA-MDI BID, or matching placebo</td>
<td>3</td>
<td>2 replicate randomized, double-blinded, double-dummy, placebo-controlled, parallel-group, 24-wk studies</td>
<td>2,100 patients 18–75 y old with moderate symptomatic asthma</td>
<td>medium-dose ICS (budesonide 400–800 µg or equivalent) peak FEV&lt;sub&gt;1&lt;/sub&gt;(0–3h), trough FEV&lt;sub&gt;1&lt;/sub&gt;, ACQ-7 responder rate&lt;sup&gt;2&lt;/sup&gt;, FEV&lt;sub&gt;1&lt;/sub&gt; and FVC, adverse events, vital signs, PEFA&lt;sub&gt;r&lt;/sub&gt;, PEFA&lt;sub&gt;p&lt;/sub&gt;, ACQ-7, AQLO, adverse events, vital signs</td>
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<td>Ohta et al, 2015&lt;sup&gt;40&lt;/sup&gt;; NCT01340209</td>
<td>inhaled tiotropium Respimat 5 or 2.5 µg or placebo Respimat QD (evening dosing)</td>
<td>3</td>
<td>randomized, double-blinded, placebo-controlled, parallel-group, 52-wk study</td>
<td>285 Japanese patients 18–75 y old with moderate symptomatic asthma</td>
<td>medium-dose ICS (budesonide 400–800 µg or equivalent) ± LABA peak FEV&lt;sub&gt;1&lt;/sub&gt;(0–3h), trough FEV&lt;sub&gt;1&lt;/sub&gt;, peak FVC&lt;sub&gt;0&lt;/sub&gt;&lt;sub&gt;–3h&lt;/sub&gt;, PEFAM, PEFPM, ACQ-7, AQLQ, adverse events, vital signs</td>
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<td>Vogelberg et al, 2014&lt;sup&gt;41&lt;/sup&gt;; NCT01122680</td>
<td>inhaled tiotropium Respimat 5, 2.5, or 1.25 µg or placebo Respimat QD (evening dosing)</td>
<td>2</td>
<td>randomized, double-blinded, placebo-controlled, dose-ranging, incomplete-crossover, 12-wk study</td>
<td>105 adolescents 12–17 y old with moderate symptomatic asthma</td>
<td>medium-dose ICS ± leukotriene receptor antagonists peak FEV&lt;sub&gt;1&lt;/sub&gt;(0–3h), trough FEV&lt;sub&gt;1&lt;/sub&gt;, FEV&lt;sub&gt;1&lt;/sub&gt; AUC(0–3h), PEFA&lt;sub&gt;r&lt;/sub&gt;, PEFA&lt;sub&gt;p&lt;/sub&gt;, ACQ-7, adverse events, vital signs</td>
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<tr>
<td>Vogelberg et al, 2015&lt;sup&gt;42&lt;/sup&gt;; NCT01383499</td>
<td>inhaled tiotropium Respimat 5, 2.5, or 1.25 µg or placebo Respimat QD (evening dosing)</td>
<td>2</td>
<td>randomized, double-blinded, placebo-controlled, dose-ranging, incomplete-crossover, 12-wk study</td>
<td>101 patients 6–11 y old with moderate symptomatic asthma</td>
<td>medium-dose ICS (budesonide 200–400 µg or equivalent) ± leukotriene receptor antagonists peak FEV&lt;sub&gt;1&lt;/sub&gt;(0–3h), trough FEV&lt;sub&gt;1&lt;/sub&gt;, FEV&lt;sub&gt;1&lt;/sub&gt; AUC(0–3h), peak FVC&lt;sub&gt;0&lt;/sub&gt;&lt;sub&gt;–3h&lt;/sub&gt;, trough FVC, FVC AUC(0–3h), PEFA&lt;sub&gt;r&lt;/sub&gt;, PEFA&lt;sub&gt;p&lt;/sub&gt;, PEFA&lt;sub&gt;r&lt;/sub&gt;, PEFPM, individual FEV&lt;sub&gt;1&lt;/sub&gt; measurements, FEV&lt;sub&gt;25&lt;/sub&gt;–75&lt;sub&gt;%,&lt;/sub&gt; ACQ-7, PAQLQ(S), adverse events</td>
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Abbreviations: ACQ, Asthma Control Questionnaire; ACQ-5, 5-question Asthma Control Questionnaire; ACQ-6, 6-question Asthma Control Questionnaire; ACQ-7, 7-question Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; ASUI, Asthma Symptom Utility Index; AUC(0–3h), area under the curve within 3 hours after dose; BID, twice daily; CRTH2, chemoattractant receptor-homologous molecule expressed on T-helper type 2 lymphocytes; FEF<sub>25–75%</sub>, forced expiratory flow between 25% and 75%; FEV<sub>1</sub>, forced expiratory volume in 1 second; FVC<sub>0</sub><sub>–3h</sub>, forced vital capacity within 3 hours after dose; FVC, forced vital capacity; HFA-MDI, hydrofluoroalkane metered-dose inhaler; ICS, inhaled corticosteroids; IgE, immunoglobulin E; IL, interleukin; LABA, long-acting β<sub>2</sub>-agonist; LAMA, long-acting muscarinic antagonist; ND, not defined; PAQLQ(S), Standardised Paediatric Asthma Quality of Life Questionnaire; peak FEV<sub>1</sub>(0–3h), peak forced expiratory volume in 1 second within 3 hours after dose; PEF, peak expiratory flow; PEF<sub>Δ</sub><sub>90</sub>, morning peak expiratory flow; PEFA<sub>p</sub>, evening peak expiratory flow; QD, once daily; SABA, short-acting β<sub>2</sub>-agonist; SGRQ, St George’s Respiratory Questionnaire.

<sup>1</sup>Excluding rescue medication.

<sup>2</sup>Primary end point.
References


[15] van Schalkwyk E, Strydom K, Williams Z, et al. Roflumilast, an oral, once-daily phosphodiesterase 4 inhibitor, attenuates allergen-induced asthma re-


